

Low Physical Activity and Obesity: Causes of Chronic Disease or Simply Predictors?

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ABSTRACT

TELFORD, R. D. Low Physical Activity and Obesity: Causes of Chronic Disease or Simply Predictors? *Med. Sci. Sports Exerc.*, Vol. 39, No. 8, pp. 1233–1240, 2007. **Background and Purpose:** Many studies have shown associations between risk of morbidity and mortality with both obesity and low physical activity (PA), but association does not imply causality. Moreover, there is an inverse relationship between PA and obesity; therefore, controlling for one of these factors when investigating the risk associated with the other is essential. The purpose of this review is to determine whether low PA and obesity actually cause metabolic dysfunction and chronic disease, especially type 2 diabetes (T2D), rather than simply operating as predictors or markers. **Methods:** The case for causality is strengthened if the following two conditions are satisfied: first, that significant associations between obesity or low PA and risk persist after controlling appropriately; and second, that the physiological mechanisms by which obesity or low PA may exert a causal effect are clearly established. The studies examined include those that have used cardiorespiratory (CR) fitness as a surrogate measure for PA, thus also providing evidence for low CR fitness as an independent risk factor in its own right. **Results and Conclusions:** Low PA and poor CR fitness are independent predictors of mortality related to type 2 diabetes and chronic disease in general. Together with well-demonstrated mechanisms, there is strong evidence that low PA and low CR fitness are direct, independent causes of metabolic dysfunction and type 2 diabetes. Despite some reports to the contrary, there is evidence that both general and visceral obesity are predictors of mortality and morbidity after controlling for PA. However, in the absence of established mechanisms, evidence is insufficient to conclude that either general or visceral obesity is a direct, independent cause of metabolic dysfunction or type 2 diabetes. **Key Words:** EXERCISE, FITNESS, CARDIOVASCULAR DISEASE, CYTOKINES, RISK FACTORS, PREVENTION

It is well established that obesity and level of physical activity (PA) are negatively correlated, so any attempt to demonstrate one of these as an independent cause of chronic disease, such as type 2 diabetes (T2D), requires control of the other. Numerous studies have investigated the association of body fat with mortality and morbidity without any control for the effects of PA, precluding inferences related to causality (5). Even a recently published review of the hazardous aspects of body fat (57) does not consider PA a potentially confounding factor. Consequently, concern has been expressed that the risks of overweight and

obesity have been overemphasized (7,10). The recent meta-analysis of the risks associated with a high body mass index (BMI, body mass in kilograms divided by the square of height in meters) in patients with coronary artery disease, indicating mortality risk to be lower in overweight compared with normal and underweight categories (54), exemplifies current confusion in this area.

This article involves two types of studies in developing arguments for the effects of PA and obesity, causal or otherwise. First, large-sample observational studies of overall mortality risk that statistically controlled for PA and obesity were reviewed. It is acknowledged that mortality risk associated with low PA and obesity is related mainly to chronic degenerative disease in general and not just T2D, CV disease being the other major contributor. However, mortality risks attributable to T2D and CV are certainly not independent; not only do these diseases share early elements of metabolic dysfunction, but one of the most serious consequences of T2D is CV disease. Consequently, should appropriately controlled studies indicate little overall mortality risk associated with either low PA or obesity, then any case that they cause T2D would be severely weakened.

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Submitted for publication December 2006.

Accepted for publication March 2007.

0195-9131/07/3908-1233/0

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DOI: 10.1249/mss.0b013e31806215b7

Some observational studies have specifically investigated risk of T2D and insulin resistance (IR) and are cited along with the studies of overall mortality. On the other hand, this article does not involve a comprehensive review of the relative influence of low PA and obesity on CV disease, because these risk factors may influence CV disease through pathways other than metabolic disturbances shared with T2D.

Secondly, physiological studies of potential mechanisms by which low PA and obesity may cause metabolic dysfunction, IR, and T2D are reviewed. It is reasoned that if mechanisms by which low PA and/or obesity increase metabolic dysfunction and IR are clearly demonstrated, and solid associations of the variable in question with mortality and morbidity risk are apparent in controlled studies, then the case for causality is strong. Specific questions addressed are summarized in Table 1.

The electronic database PubMed was used. Key words were physical activity, obesity, body mass index, visceral adipose tissue, fitness, and exercise in conjunction with mortality, type 2 diabetes, and insulin resistance; articles were searched from July 1995 through July 2006. Only peer-reviewed journals were considered with controls for PA when obesity was being examined, and vice versa.

MEASURING PHYSICAL ACTIVITY AND OBESITY

An underlying problem is the difficulty in measuring PA and body fat with acceptable validity and reliability. As commented in editorials (5,6), self-report questionnaires usually involved in large-sample studies not only involve inaccurate recall, but they may not include appropriate questions to capture all relevant activities, particularly nonrecreational PA. Furthermore, wide variation in energy expenditure among individuals undertaking a particular activity adds to any error of estimation of PA.

Estimations of obesity in large-sample studies are usually confined to measuring surrogates of obesity such as body weight and BMI. Although they incorporate nonfat mass, overweight and BMI are still likely to be reasonable indicators of overfatness (especially changes) in nonathletically trained mature groups where muscle mass does not change appreciably. Given the arbitrary nature of defining when increased adiposity constitutes obesity, some authors have investigated relationships between mortality/morbidity and an index of body composition such as BMI to draw conclusions as to the effect of obesity. Other authors have categorized body fat levels, classifying subjects as normal,

overweight, or obese with BMI levels of < 25, 25–30, and > 30, respectively. Both approaches are incorporated in the current review of evidence for obesity as a risk factor.

Estimates of obesity, despite their limitations, are likely to be more objective in population-based studies and, therefore, probably more valid and reliable than subjective estimates of PA. Supporting this premise is the view that self-reported PA is “crude and imprecise” and that overreporting, together with difficulty in adjusting for socioeconomic factors, leads to underestimation of the effects of PA (27).

Some studies have substituted a measure of cardiorespiratory (CR) fitness in an attempt to circumvent the problems associated with measuring PA. This has usually been a progressive treadmill test to near exhaustion (12,40). Despite well-based arguments that CR fitness might be treated as a risk factor in its own right, being partly genetically controlled (37), acceptable relationships between CR fitness and PA, especially in older groups, provide support for CR fitness as a useful surrogate of PA (48). This review focuses predominantly on the relationships between PA and health outcomes, with relationships between CR fitness and health providing supporting evidence. However, the latter relationships also provide direct evidence of low CR fitness *per se* as a risk factor, as well as supporting the case for low PA. In passing, it is notable that, along with CR fitness, neither low PA nor obesity are confined to influence by environmental factors alone. There is solid evidence that genotype plays a significant interactive role, with an inherited higher proportion of type 1 muscle fiber a mediating factor predisposing both low PA and obesity (30).

Do low PA and low CR fitness increase risk of mortality attributable to chronic disease and type 2 diabetes? The following studies complied with the selection criterion of applying appropriate control. Lee et al. (40) observed 21,925 men for an average of 8 yr, subjects having been assessed for body composition and by a treadmill test. After appropriate adjustments for confounding factors, unfit, lean men had double the risk of all-cause mortality of fit, lean men, and they were also at higher risk of all-cause mortality than were obese men who were classified as fit. In another prospective study, 9925 women were observed for 11 yr; after adjustments for BMI, there was, again, a significant inverse relationship between CR fitness and mortality risk (20). Another study (60) involved 2506 men and 2860 women, with mortality recorded for 20 yr; a protective effect of fitness independent of fatness was again reported. In the Nurses' Health Study (45), a significant, graded relationship between PA and CV disease mortality was found in both nonobese and obese nurses. Similar findings of the effect of PA independent of BMI were reported in males (63).

An investigation of 2316 men with diabetes during 16 yr found that low-fit individuals were at 2.7 times the risk of dying of CV disease compared with the normal-weight men of high fitness, irrespective of whether they were of normal

TABLE 1. Specific questions addressed in this review.

- Does low physical activity, after adjustment for obesity, increase the risk of mortality and specific morbidity related to type 2 diabetes?
- Does obesity, after adjustment for physical activity, increase the risk of mortality and specific morbidity related to type 2 diabetes?
- Are there established mechanisms underlying the role of obesity as a causal risk factor for metabolic dysfunction, insulin resistance, and type 2 diabetes?
- Are there established mechanisms underlying the role of physical activity in the prevention of metabolic dysfunction, insulin resistance, and type 2 diabetes?

weight, overweight, or obese (12). Two further studies provide evidence that PA plays an important role in preventing T2D independent of obesity. Firstly, PA and blood insulin concentrations were negatively correlated in two high-risk populations of differing levels of obesity (36), and, secondly, increasing levels of PA coincided with decreased incidence of diabetes after adjusting for BMI (67). Finally, free-living activity energy expenditure (assessed using doubly labeled water) was strongly associated with mortality risk (44); in controlling for BMI, this study produced good evidence that low to moderate energy expenditure reduces mortality risk in older men and women.

Of studies focusing on obesity in the next section, some also investigated the effect of PA after controlling for BMI. In these studies, without exception, mortality rates were directly related, some in a graded manner, to reduced PA or fitness (18,27,31,42,69).

Summing up, there is consistent evidence from observational studies that low PA is a predictive risk factor for T2D and mortality that operates independently of obesity.

Does obesity increase risk of T2D or mortality attributable to chronic disease? Several studies involving adjustments for PA provide evidence that obesity, or a surrogate thereof, predicts risk of mortality. The follow-up of the first National Health and Nutrition Examination Survey involved 9790 subjects during a 17-yr period (18), and CV disease mortality was related in a graded manner with overweight and obesity, after controlling for PA. The Nurses Health Study report, which involved 88,393 women, reported 889 deaths attributable to coronary heart disease (42), and in a joint analysis of BMI and PA, BMI was a significant risk factor. The Women's Health prospective cohort study (70) involved 37,878 women with 7 yr of follow-up, and BMI was found to be a risk factor for diabetes, independent of PA.

A Finnish population-based prospective study (27) monitored 18,892 men and women ages 25–74 yr for a mean of 10 yr. The researchers concluded that both general and abdominal obesity predict the risk of CV disease among middle-aged men and women, independently of PA. One other study was clearly titled “Fatness is a better predictor of CV disease risk factor profile than aerobic fitness in healthy men” (11). However, it has been claimed that the data should have been interpreted to conclude the opposite—that aerobic fitness was the better predictor (2)—and readers are invited to form their own opinions.

In contrast to low PA, some observational studies of risk attributable to obesity have failed to demonstrate significant relationships. For example, one group (31) observed 19,173 men for 10 yr; after including CR fitness in the model, the risks associated with obesity on metabolic syndrome were no longer significant. An intervention-based study (17) involved 423 men with impaired glucose tolerance, and one group was provided with a diet and exercise program while another underwent routine treatment. Whereas mortality was reduced by the intervention, change in BMI was not a

significant factor. Finally, of the studies described in the previous section concerning PA, three also analyzed risks associated with obesity after controlling for PA or CR fitness. In the first, BMI was not significantly correlated with mortality (60); the second study (20) found that BMI quintiles tended to be associated with mortality outcomes after controlling for fitness, but they often were not statistically significant; the third study reported that the relationship between BMI and mortality was almost eradicated after adjusting for CR fitness (12).

In summary, several studies provide evidence of the independent nature of the relationship between obesity and mortality. However, the fact that several other studies were unable to demonstrate any significant risk associated with BMI suggests that obesity as a predictor of mortality may vary according to the sample studied (Table 2).

Are there established mechanisms underlying the role of increased adiposity as a causal risk factor?

Elevated concentration of free fatty acids (FFA) is implicated with the onset of insulin resistance (32) and leads to hypertriglyceridemia and a range of adverse changes in the vascular endothelium (29) that are similar to key early steps in atherogenesis. One fundamental consideration for obesity playing a causal role in T2D is that adipocytes secrete FFA into the bloodstream, resulting in chronically elevated plasma FFA. Another consideration relates to the endocrine role of adipose tissue (AT), in that cytokine secretions from adipocytes induce a chronic low-grade proinflammatory state, which, in turn, plays a role in metabolic dysfunction. A third consideration is that the influence of AT may vary according to its site. Visceral AT has been suggested to be more significant in elevating blood FFA concentration, whereas peripherally located AT might act as a buffer or sink for circulating fats (22). The seemingly paradoxical corollary of the latter is that a limitation in adipocyte-storage capacity may lead to impaired insulin resistance (53,62).

Chronically increased plasma FFA and insulin resistance: increased secretion from fat or decreased use by muscle?

On the basis of previously demonstrated relationships between decreased lipid oxidation and development of obesity, Colberg and colleagues (13) set out to test whether muscle insulin resistance is attributable to increased FFA delivery to the muscle cell or an impaired ability of the muscle to oxidize FFA. Their leg-balance design involved premenopausal women of varying body fat distribution. Whereas quantity of visceral AT was a clear marker of skeletal muscle insulin resistance, no evidence emerged to support the hypothesis that muscle

TABLE 2. Are physical activity (PA) and obesity independent markers of mortality?

- Large-sample, community-based observational studies provide consistent evidence to indicate that low PA is a predictive risk factor (marker) of mortality, independently of obesity.
- Despite some conflicting reports, the weight of evidence suggests that increased obesity is a predictive risk factor (marker) of mortality, independently of PA.

tissue insulin resistance in women with visceral obesity is caused by excess secretion of FFA into the plasma. Instead, increased insulin resistance in the muscles of the visceraally obese women was associated with reduced capacity for FFA use in skeletal muscle (a consequence of low PA).

Colberg's group (13) reminds us that among healthy, lean individuals there is efficient uptake and oxidation of plasma FFA in skeletal muscle during the postabsorptive state. Their finding that both fasting FFA metabolism and insulin-stimulated glucose metabolism are correlated with activity of citrate synthase suggests that postabsorptive use of FFA by muscle is "integrally linked to phenotypic expression of insulin sensitivity." The authors recognize cited support for this concept: first, a positive relationship between fasting activity of muscle lipoprotein lipase and insulin sensitivity, and, second, exercise enhances insulin sensitivity of muscle along with its capacity for lipid use.

Recent evidence of the dominant role of muscle in the control of plasma FFA in healthy individuals is provided through the concept of *metabolic flexibility* (MF); this term describes optimal metabolic characteristics (61). Metabolically flexible individuals respond to fasting with increased reliance on fat oxidation; this response is suppressed by insulin, which, in turn, suppresses fat oxidation, switching intramuscular substrate use to glucose. A *flat* metabolic response pattern is characteristic of the metabolic syndrome that involves insulin resistance. Ukropcova and coworkers (65), using *in vitro* analysis of muscle from insulin-resistant donors, found that MF in skeletal muscle cells correlated with the clinical phenotypes of the cells' donors and that defects in MF might be one of the primary events in the development of obesity and insulin resistance. This work, together with the finding that a diminished skeletal muscle reliance on fat oxidation during fasting is predictive of weight gain, provides evidence for the contention that obesity, at least in part, may be the symptom of diminished fasting fat oxidation and the result of insulin resistance, rather than its cause.

In summary, these studies indicate that the increased plasma FFA concentration link with insulin sensitivity is a consequence of depressed metabolic processes in muscle (and low PA), rather than an excess secretion of FFA by adipose tissue.

Is cytokine secretion by adipose tissue the cause of insulin resistance and chronic disease?

Low-grade inflammation has been suggested as the causal link between obesity and degenerative disease. C-reactive protein is a commonly measured marker of inflammation, although its role is controversial; one recent reviewer concludes that "to date, data from randomized, controlled trials designed to definitively test the effects of weight loss or exercise training, or both, on inflammation are limited"(47). Nevertheless, during the last two decades, there has been extensive investigation of the adipose tissue–cytokine relationship as exemplified by the review of recent advances in obesity, inflammation, and insulin resistance (3). The latter review serves to highlight deficiencies in

current understanding of the roles and modes of action of cytokines. Furthermore, the fact that PA is afforded little attention by the reviewer or the cited literature indicates that PA as a potentially confounding factor was overlooked by many researchers attempting to understand the role of obesity. On the other hand, the review by López-Soriano and coworkers (43) indicates that the expanding body of literature implicating muscle with cytokines both as a target and an endocrine tissue provides new approaches to understanding their physiological significance.

New cytokines and their isoforms are discovered each year, and this review is limited to mention of a few prominent examples. The role of leptin, despite a plethora of publications, is still uncertain in humans, but evidence of its stimulatory effect on fat oxidation (41), and evidence of leptin resistance in obesity (59), certainly implicates this cytokine with metabolic dysfunction. TNF- α is a lipolytic cytokine that also seems to play a role in the development of lipid dysfunction, but results are conflicting (68). With muscle-tissue interactions evident in animal models at least (28), current understanding of the overall physiological role of TNF- α activity in relation to obesity as a risk factor is limited. IL-6 function is also controversial. There is evidence that IL-6 effects are influenced by its tissue of origin or target, displaying inflammatory, lipolytic, and insulin-resistive induction properties when secreted by adipose tissue, the principal site of secretion at rest, but antiinflammatory properties when secreted by muscle (50), the principal site of secretion during exercise. Secretion of IL-6 has also been reported to be interactive with TNF- α , which has complicated interpretation of their specific roles (52). Adiponectin influences lipid metabolism in skeletal muscle (23) as well as in white and brown adipose tissue interacting with IL-6 and TNF- α (46). Decreased secretion of adiponectin is associated with both obesity (33) and insulin resistance (51). However, the significance of adiponectin in supporting the case for obesity as a causal risk factor requires further controlled research because physical training also increases circulating isoforms of adiponectin and mRNA expression of its receptors in muscle (8). Other uncertainties related to the role of obesity and cytokine activity are exemplified by findings of antiinflammatory properties of human fat (15), and some cytokines are now implicated with cell proliferation in muscle and adipose tissue (50); each of these factors contributes to the balance of influence on insulin sensitivity.

In summary, although there is evidence that cytokine secretion from adipose tissue exerts widespread influence on human physiology, the overall significance of this in terms of risk of metabolic dysfunction and T2D is not clear. More research is required to understand net whole-body endocrine effects influenced by the interactive roles of fat and muscle. This is reflected in a concluding comment from a recent review (19): "The field is too young to allow for therapeutic implications ... we still need to understand the exact role of adipose tissue in modulating immunity and inflammation."

Surgical removal of body fat. Some arguments in support of a causal role of obesity in CV disease and T2D have been based on findings of positive outcomes after surgical removal of fat. However, as pointed out by the recent work of Klein and colleagues (35), the interpretation of data from studies involving the effect of surgical removal of body fat on health-related measures often has been confounded by, among other factors, ensuing lifestyle factors. These workers attempted to overcome confounding issues before and after liposuction in 15 obese females with regular visits to the patients, stressing the importance of maintaining body weight with usual exercise and appropriate dietary patterns. Twelve weeks after the liposuction and the aspiration of an average of 10 kg of adipose tissue, there were no effects on insulin sensitivity in skeletal muscle, liver, or adipose tissue, blood pressure, fasting plasma glucose, insulin, or lipid concentrations. As noted by Campos and coworkers (10), these results strongly suggest that the diet and exercise modification *per se*, rather than any subsequent loss of body fat, are the causes of the observed health improvements.

Is visceral or peripheral adiposity a cause of metabolic dysfunction? There are conflicting results and ongoing debate as to the relative influences of visceral and subcutaneously located fat stores (14). The case for visceral AT as an independent causal risk factor warrants investigation because of the significance of correlations with metabolic dysfunction and mortality (66). These correlations are often, but not always (27), more significant than correlations with total body fat (4,38). Given that exercise is closely associated both with visceral fat use (55) and plasma FFA concentration, controlling for PA is, again, essential to making inferences, even in regard to correlations, but especially concerning causality.

The literature regarding site-specific roles of AT is not straightforward, because it has also been reported that upper-body subcutaneous fat makes the greater contribution to plasma FFA, with much lesser contributions from leg fat and visceral AT, even in persons with abdominal obesity (29). This work is consistent with that of another group (64) who found, in contrast to what they described as “rather discordant literature” on this topic, that subcutaneous fat of middle-aged women had higher lipolytic activity, including higher rates per cell.

An interesting and different perspective on peripheral body fat is provided by the adipose tissue-buffer hypothesis. Peripherally sited adipocytes have been suggested to act as a buffer for circulating fats, offsetting the tendency for ectopic deposition into muscle, liver, and pancreas, a process associated with insulin resistance (39). According to this hypothesis, fat cells not filled to capacity may provide a protective effect. This is consistent with the finding that enlarged adipocytes, but not percent body fat, was found to be positively correlated with insulin resistance (71). It also provides some theoretical support, independent of any role of PA, for the findings of reduced risk of

mortality in overweight compared with leaner individuals (12,20,31,40), and it may offer part of the explanation for findings that low BMI has been associated with increased risk of morbidity and mortality (25,54).

In summary, the current evidence for obesity as a causal risk factor for metabolic dysfunction and insulin resistance is inconclusive, both in terms of its role in increasing plasma FFA concentration and its role in low-grade inflammation through the cytokines. That several studies actually suggest lowered risk with increasing BMI, with some authors suggesting a benefit in possessing greater storage capacity in adipose tissue, indicates the complexity of this area of investigation. As one recent reviewer put it, “Obesity increases the risk of metabolic syndrome, but as obesity is neither necessary nor sufficient to cause the syndrome, there is considerable interest in identifying obesity-independent pathways” (21).

Are there established mechanisms underlying physical activity as a causal risk factor? In contrast to the controversies and difficulties of interpretation regarding mechanisms by which obesity might impact insulin resistance, T2D, and mortality, the case for PA is more straightforward. The finding that muscle oxidative capacity, in itself dependent on PA, is directly related to insulin sensitivity has been addressed above. Moreover, there have been many informative reviews on the preventive and therapeutic properties of PA (9,49), including the more specific review relating to mechanisms by which exercise impacts insulin resistance (26). In light of such reviews and in the interest of concision, the current article includes a summary of mechanisms together with relevant references in Table 3.

One relatively new area of investigation is singled out for brief discussion because it adds support for the above premise that increased capacity for FFA oxidation (and, therefore, CR fitness and PA) directly improves insulin sensitivity. The nuclear peroxisome proliferator-activated receptors (PPAR) are activated by lipids, including FFA, which in turn bind to specific regions of the promoters of many genes, including some concerned with lipid metabolism, modulating their expression. In their review, López-Soriano and coworkers (43) describe new interest in PPAR- δ , the least studied of the three PPAR isoforms. Animal models investigating increased PPAR- δ activity indicate reversals of insulin sensitivity, as well as improved lipid profiles—hence, reduced risk of CV disease. Skeletal

TABLE 3. Mechanisms by which physical activity reduces risk of metabolic dysfunction and type 2 diabetes.

- Increased muscle insulin sensitivity (GLUT-4 expression and mobility) (48)
- Insulin-independent action on GLUT-4-induced glucose transport (56)
- Increased insulin sensitivity and glucose uptake in adipose tissue (58)
- Clearance of both blood free fatty acids and glucose via increased type 1 fibers (29), mitochondria, oxidative capacity numbers, glycogen synthase activity (18), and regulation of oxidative phosphorylative genes (14,15,28)
- Antioxidant protective effect of nitric oxide (26) and improved endothelial function (36)
- Dose-dependent reduction of body fat, facilitating further exercise (59)

TABLE 4. Mechanisms by which obesity and low physical activity (PA) reduce risk.

- Mechanisms of obesity are not obvious, because available evidence suggests that the plasma free fatty acid link with insulin resistance is a consequence of depressed metabolic processes in muscle (and low PA/fitness) rather than secretion of free fatty acids by adipose tissue.
- The net effects of cytokines secreted in adipose tissue are inconclusive.
- Mechanisms of low PA/fitness are clear, because available evidence indicates well-demonstrated depression of muscle insulin sensitivity of muscle and adipose tissue, with decreased plasma clearance of glucose and free fatty acids.

muscle is implicated in the process because PPAR- δ is the main isoform expressed in that tissue. Part of the improvement in insulin sensitivity seems to be the proliferatory effect of PPAR- δ on type 1 fibers with their higher aerobic metabolic potential (1). This partly mirrors the effect of PA and is consistent with the above findings that increased FFA use is an important mechanism by which PA reduces risk of metabolic dysfunction.

Of the mechanisms by which PA and CR fitness reduce risk of metabolic dysfunction, insulin resistance, and T2D (Table 3), one area warrants explanation. The antioxidant effect of PA, through stimulation of superoxide dismutase production (24), protects nitric oxide (NO) and initiates events to increase parasympathetic tone, shear stress, NO production, and vascular endothelial growth factor (34). The positive effect PA exerts on endothelial function and microcirculatory control provides indirect supportive evidence for its role in decreasing the risk of chronic degenerative disease.

In summary, several mechanisms by which PA, but also CR fitness *per se*, reduce risk of metabolic dysfunction, IR, and T2D are well demonstrated. That muscle is intimately involved with metabolic disorders should not come as a surprise, because muscle tissue accounts for about 40% of body mass and 80–90% of insulin-stimulated glucose uptake (16). Certainly, studies have demonstrated that weight loss is not necessary for individuals to benefit from

the effects of physical activity on glucose tolerance and insulin sensitivity (9) (Table 4).

FINAL COMMENT

The scientific literature indicates consistent findings of strong associations of PA (and poor CR fitness) with mortality and with morbidity associated with T2D, after controlling for obesity and other potentially confounding factors. Furthermore, there are several well-demonstrated mechanisms by which PA directly influences insulin sensitivity. Collectively, these findings indicate that low PA and low CR fitness are not just predictors, but direct causes of metabolic dysfunction and the morbidity and mortality associated with T2D.

By contrast, there is little evidence that overfatness and obesity (adjusting for any effect of reduced PA) actually cause T2D. Observational studies suggest that obesity, including viscerally sited obesity, is most appropriately categorized as a marker or predictive (noncausal) risk factor for T2D, although, in contrast to PA, several studies were not able to detect any significant correlation after controlling for PA.

The findings are consistent with the premise that PA is of direct benefit, perhaps even essential to preventive and curative medicine in relation to insulin resistance and T2D. On the other hand, there is little support for the widely held belief that increasing body fat *per se* actually causes metabolic dysfunction, T2D, or increases the risk of mortality, and there is little evidence that losing fat *per se* has any direct benefit as a cure. In terms of T2D, these conclusions should not be interpreted as condoning obesity, because obese individuals are less likely to engage in a lifestyle incorporating sufficient physical activity to maintain optimal metabolic health.

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